Research to Practice

THE USE OF PLACEBO-CONTROLLED CLINICAL TRIALS FOR THE APPROVAL OF PSYCHIATRIC DRUGS:

Part I—Statistics and the Case for the "Greater Good"

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On more than one occasion when I have presented data from a phase III (pre-approval), placebo-controlled, randomized, clinical trial of some psychiatric drug, I have been met with shock and incredulity from some of the psychiatrists in the audience that such studies, ones where psychiatric patients may receive placebos, are allowed to be conducted. The reality is that not only are such studies "allowed," they are all but required for US Food and Drug Administration (FDA) approval of a new psychiatric drug. The regulatory process for new drug approval in this country nearly requires that a pharmaceutical manufacturer conduct placebo-controlled studies in which psychiatric patients are washed off of their approved medication and randomized to treatment arms that include a placebo. Without any exceptions of which I am aware, all psychotropic medications, including all antidepressants, mood stabilizers, and antipsychotics, currently approved by the FDA have earned that approval through such randomized, controlled trials using placebo. Since there seems to be much misinformation about how psychotropic medications become approved, I have opted to shed some light on this topic in two parts of this Research to Practice column. In this first part, I focus on the scientific and statistical considerations that have established placebo-controlled studies as the *de rigueur* pathway to regulatory approval for psychiatric drugs in the United States. This will address the ethical nature of placebo studies from a "global" or "greater good" perspective, but not necessarily from the vantage point of any given individual subject who may participate in a clinical trial. In the upcoming Part 2 on this topic, I will address the little known and underappreciated design elements in contemporary, industry-sponsored, placebo-controlled, clinical trials that often make them ethically legitimate options for some individual patients despite inherent risks involved.

The arguments against including placebo in clinical trials that evaluate new psychiatric medications have been presented in many previous papers.[1–3] In essence, the argument is an ethical one and can be boiled

down to the notion that "washing off" patients with high-risk psychiatric illnesses and then randomly assigning them to a treatment arm that might consist of a placebo exposes those patients to significant risks and, thus is not ethically justifiable since there are efficacious, approved medications available. Those who make this case typically advocate for new drugs to be approved using clinical trials that compare investigational medication with established approved drugs instead of placebo. Advocates of this approach argue that if an investigational new drug can demonstrate equivalent or superior efficacy and safety compared to an approved drug, then it should warrant approval by the FDA. This research approach for approval has been termed *equivalence* or *noninferiority* and stands in contrast to the *superiority* criteria currently required by the FDA. In this approach, an investigational drug must demonstrate statistical superiority to a comparator. While the comparator does not necessarily need to be a placebo, for practical reasons it almost always is.

Prima facie, the ethical case for the noninferiority approach seems very compelling. However, all is not what it seems on the face of it, and a little scratching beneath the scientific surface reveals a much more complex issue.

The FDA, by policy, will not accept a noninferiority study as basis for approval of a new psychotropic drug for the US marketplace. Why would the FDA, whose mandate is to protect the health of US citizens, reject a drug approval approach that would spare patients the risk of nonactive treatment? For detailed explanations of the FDA's position and the statistical reasoning supporting it, I refer readers to papers authored by Laughren[4] and Streiner.[5] The rationale behind the FDA's stance lies in the science of clinical research. In the parlance of the field, a clinical trial that compares an established drug and an experimental drug but has no placebo arm lacks proof of *assay sensitivity*, a control condition necessary to verify that any particular study, as it was designed and executed, represented an effective scientific assay that was capable of revealing the efficacy of drugs tested. If an experiment lacks proof of assay sensitivity, then it is not possible to know if an equivalency outcome, in which both drugs had comparable effects, was due to both drugs being efficacious or simply a deficiency in the assay (the experiment) to reveal the true nonequivalence between the drugs. A placebo arm provides an indicator of assay sensitivity to a head-to-head comparison of experimental drug to an established drug. If the established drug, for example an antidepressant, separates from placebo as expected, one can be confident that the study was an appropriate assay for detecting antidepressant medication effects; one could be confident in findings revealed for the experimental antidepressant tested in the same study. On the other hand, if the established drug fails to separate from placebo, it indicates that the study was an inadequate assay for detecting antidepressant medication efficacy and it is considered a failed study, which is not the same as a negative study, due to way it was designed or executed. No conclusion can be drawn about the investigational drug in a failed study.

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It is reasonable to forgo proof of assay sensitivity, and thus a placebo arm, if one can be confident that the established drug used as comparator consistently exhibits efficacy from historical experience. That is to say, if a drug consistently separated from placebo in 20 out of 20 previous studies, then it would be reasonable to assume it is producing supraplacebo effects in the 21st study without including a placebo to prove that fact. Here, however, is the rub. Since psychiatric illnesses are highly prone to placebo-induced, acute improvement of symptoms, even established medications often fail to separate from placebo. According to an FDA analysis of well-designed schizophrenia studies in its database, antipsychotics that ultimately were approved and established to be efficacious for schizophrenia failed to separate from placebo approximately 25 percent of the time.[4] The placebo separation failure rate for established antidepressants from the same FDA database was 46 percent.[4]

Therefore, if an investigational drug demonstrated equivalence to an approved drug in a noninferiority study of a psychiatric condition, it would be impossible to know if this

outcome was because both drugs were efficacious or because both lacked efficacy in that study (i.e., both produced effects that were not significantly superior to placebo). This would lead to what is referred to as a "type I error," attributing efficacy to a treatment when in fact it did not have true efficacy. In essence, such a false positive would occur in one out of every four studies in which an inefficacious antipsychotic was tested and close to half of the time that a inefficacious antidepressant was tested. The consequence, therefore, of adapting a noninferiority test for psychiatric drug approval would be, predictably, the erroneous approval of inefficacious medications that, in turn, would lead to thousands of patients being treated with a medication that had no more efficacy than placebo. The FDA's position is that there is substantially greater potential for harm from approving a inefficacious medication compared to the risk posed to consenting individual subjects who take a calculated, informed risk of being placed on placebo.

There are also other problems with the noninferiority approach to drug approval. For example, to be adequately powered noninferiority studies requires recruitment of many more subjects than superiority studies, and many more subjects would be exposed to the investigational medication and any possible adverse effects it may have than would be in a placebo-controlled superiority study. Moreover, because the goal in a superiority study is to demonstrate a presumed difference between the investigational drug and placebo, an enormous amount of resources are directed into developing good study design and clean study execution by the pharmaceutical sponsors. This is because sloppiness increases the statistical "noise" that reduces the assay sensitivity of a study and its ability to reveal the difference between a tested drug and placebo. Rigorous confirmation of diagnosis, exclusion of concomitant medication or concomitant medical disorders, and incorporating placebo "run-in" phases to ferret out patients who are likely to improve spontaneously are examples of ways pharmaceutical sponsors increase the assay sensitivity of a clinical trial. In contrast, success for the pharmaceutical sponsor in a noninferiority study would be demonstration of equivalence between the investigational drug and the established drug. As such, the incentive for pharmaceutical companies shifts away from rigorous design and execution, and there is concern that this would lead to shifts in conduct of the clinical trials even if this was not deliberate.

As a result of these problematic issues surrounding noninferiority studies, the FDA's policy has consistently been that it can only approve potential psychotropic drugs that demonstrate clear superiority to a control comparator. This control comparator need not be a placebo; however, since the ability to demonstrate superiority relative to an approved, active medication is very difficult to achieve, pharmaceutical manufacturers almost always incorporate a placebo arm.

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